

# PATENT COOPERATION TREATY

From the  
INTERNATIONAL SEARCHING AUTHORITY

# PCT

To: .

see form PCT/ISA/220

## WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing

(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference  
see form PCT/ISA/220

### FOR FURTHER ACTION

See paragraph 2 below

International application No.  
PCT/IB2004/004335

International filing date (day/month/year)  
06.12.2004

Priority date (day/month/year)  
05.12.2003

International Patent Classification (IPC) or both national classification and IPC  
C07K14/705, G06F19/00

Applicant  
UNIVERSITY OF GRONINGEN

### 1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

### 2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

### 3. For further details, see notes to Form PCT/ISA/220.

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**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

10/581856  
IAP2 Rec'd PCT/PTO 05 JUN 2006  
International application No.  
PCT/IB2004/004335

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**Box No. I Basis of the opinion**

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1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
  - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
  - a. type of material:
    - ☒ a sequence listing
    - ☒ table(s) related to the sequence listing
  - b. format of material:
    - ☒ in written format
    - ☒ in computer readable form
  - c. time of filing/furnishing:
    - ☐ contained in the international application as filed.
    - ☐ filed together with the international application in computer readable form.
    - ☒ furnished subsequently to this Authority for the purposes of search.
3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

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**Box No. II Priority**

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1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43bis.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/IB2004/004335

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**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

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**1. Statement**

Novelty (N)	Yes: Claims	8, 10, 12-13, 15, 17, 28, 34, 41-53, 60-62
	No: Claims	1-7, 9, 11, 14, 16, 18-27, 33, 35-38, 54-59
Inventive step (IS)	Yes: Claims	8, 10, 12-13, 15, 17, 28, 34, 41-53, 60-62
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-62
	No: Claims	

**2. Citations and explanations**

**see separate sheet**

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**Box No. VIII Certain observations on the international application**

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The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

**Re Item I**

**Basis of the report**

Reference is made to the following documents:

- D1: WO 03/029420 A (GENENTECH, INC; KELLEY, ROBERT F; LINDSTROM, STEPHANIE H) 10 April 2003 (2003-04-10)
- D2: WO 99/36535 A (GENENTECH, INC; ASHKENAZI, AVI, J; KELLEY, ROBERT, F; O'CONNEL, MARK,) 22 July 1999 (1999-07-22)
- D3: WO 01/00832 A (GENENTECH, INC) 4 January 2001 (2001-01-04)
- D4: WO 88/06625 A (CETUS CORPORATION) 7 September 1988 (1988-09-07)
- D5: WO 2004/001009 A (GENENTECH, INC; HYMOWITZ, SARAH; KELLEY, ROBERT, F; LINDSTROM, STEPHAN) 31 December 2003 (2003-12-31)
- D6: VAN DER SLOOT ALMER M ET AL: "Stabilization of TRAIL, an all-beta-sheet multimeric protein, using computational redesign." PROTEIN ENGINEERING, DESIGN & SELECTION : PEDS. SEP 2004, vol. 17, no. 9, September 2004 (2004-09), pages 673-680, XP002324633 ISSN: 1741-0126

**Re Item II**

**Priority**

Since the priority document/s pertaining to the present application is/are not yet available to the IPEA, this Written Opinion/IPER has been drawn up considering the priority date as valid. D5 and D6 have/has been published between the priority date and the filing date of the present application. Thus, said documents are / document is not considered to constitute prior art in the meaning of rule 64(1)(b) PCT. However, if it turns out that the effective date of the claimed subject-matter is not the priority date then D5/D6 will become relevant to assess whether the present application satisfies the criteria set forth in Article 33(2) and (3) PCT.

**Re Item V**

**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

The instant application relates to muteins of TRAIL with desired properties (enhanced thermal stability and/or new receptor specificity). Claims are directed to positions 125, 163, 185, 187, 194, 196, 203, 205, 208, 225, 227, 230, 232, 234, 237, 239, 240, 241, 271, 272, 274, 280. Effects have been reported for E194I/I196S; D203/Q205M/Y237F; S225A; R227M; E194I/I196S/D203/Q205M/Y237F.

D1-D5 all disclose muteins for TRAIL/TNF at positions overlapping with the claimed positions. Claims 1-7, 9, 11, 14, 16, 18-27, 33, 35-38, 54-59 therefore lack novelty (Article 33(2) PCT).

The fact that certain effects/properties have not been examined for prior art products is irrelevant for assessing novelty for structurally indistinguishable products. Such properties have to be inherent. The same applies for products that may be produced by a novel process.

#### **Re Item VIII**

#### **Certain observations on the international application**

Claims 1-7, 9, 11, 14, 16, 18-27, 33, 35-38, 54-59 relate to cytokine/TRAIL muteins defined only by reference to the result to be achieved (Article 6 PCT).

The claim set encompasses 7 independent claims all directed to cytokine muteins, as such contravening the conciseness criterion (Article 6 PCT).

The claims are directed to beta sheet multimeric cytokines in general, whereas only muteins of TRAIL are disclosed (Article 6 PCT). The identification of substitutions by means of position numbers in the context of the present invention is only considered meaningful for TRAIL.

Apparently not all mutations at the indicated positions even for TRAIL result in the muteins with desired properties (see page 38 lines 23-28).

From the previous it appears as if only particular structurally defined muteins of TRAIL could form a basis for a reasonable set of claims.

The electronically filed sequence is different from the originally filed sequences at pages 55-56.